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Can self-relevant stimuli help assessing patients with disorders of consciousness?

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ABSTRACT

Emotional and self-relevant stimuli are able to automatically attract attention and their use in patients suffering from disorders of consciousness (DOC) might help detecting otherwise hidden signs of cognition.

We here recorded EEG in three Locked-in syndrome (LIS) and four Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS) patients while they listened to the voice of a family member or an unfamiliar voice during a passive. Data indicate that, in a passive listening condition, the familiar voice induces stronger alpha desynchronization than the unfamiliar one. In an active condition, the target evoked stronger alpha desynchronization in controls, two LIS patients and one VS/UWS patient. Results suggest that self-relevant familiar voice stimuli can engage additional attentional resources and might allow the detection of otherwise hidden signs of instruction-following and thus residual awareness. Further studies are necessary to find sensitive paradigms that are suited to find subtle signs of cognition and awareness in DOC patients.

1. Introduction

The gold standard in diagnosing patients with Disorders of Consciousness (DOC), i.e. Minimally Conscious State (MCS) and Vegetative State/Unresponsive Wakefulness Syndrome (VS/UWS) (Laureys et al., 2010), remains the assessment with behavioural scales such as the Coma Recovery Scale - Revised (CRS-R) (Giacino, Kalmar, & Whyte, 2004). However, due to arousal fluctuations, attentional, perceptual and motor deficits, behavioural assessment is extremely challenging in these patients and has repeatedly been linked to a high rate of misdiagnoses (Andrews, Murphy, Munday, & Littlewood, 1996; Schnakers, Vanhaudenhuyse, et al., 2009).

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The possibility to be considered as being in a MCS is based on the assumption that if a patient retains consciousness, he or she will be able to give evidence of his/her awareness, for example by purposeful motor responses. In this case, the clinician infers that the patient retains some degree of consciousness of the self and/or the environment and this likely affects the daily care and interaction with the patient.

This rationale, however, is inherently problematic as patients may not be able to "give evidence" of their awareness when suffering from severe motor deficits like quadriplegia or spasticity. When considering patients in a Locked-in Syndrome (LIS), the limitations of behavioural assessment become particularly obvious (Giacino et al., 1995). Although this syndrome is not a disorder of consciousness in a strict sense, these patients can be entirely unable to produce any motor output with even eye movements being impaired ("totally locked-in syndrome"). Therefore, from a behavioural point of view, they seem to be VS/UWS, while in fact they are both awake and aware by definition and the level of information processing and consciousness is comparable with healthy individuals (Laureys, Gosseries, & Tononi, 2015; Laureys, Owen, & Schiff, 2004; Schnakers, Majerus, et al., 2008). It has to be mentioned that, although LIS patients are considered to retain a level of consciousness comparable to that of heathy individuals, due to their clinical condition and brain damages their brain responses can differ from controls and be sometime similar to that of DOC patients (Laureys et al., 2004, 2015).

Neuroimaging methods, such as functional magnetic resonance imagery (fMRI) and electroencephalography (EEG), have thus been used to overcome the limitations of behavioural assessment (Bruno, Gosseries, Ledoux, Hustinx, & Laureys, 2011; Cruse, Monti, & Owen, 2011; Monti et al., 2010; Owen, Schiff, & Laureys, 2009) and to investigate cognitive functioning and awareness in DOC patients. As wilful command-following is a strong indicator of retained awareness and can reliably be detected via EEG recordings. Many studies have adopted designs in which patients are asked to actively perform a task and follow commands, the so-called "active paradigms" (e.g., Cruse et al., 2011, 2012; Monti et al., 2010; Owen et al., 2006; Schnakers, Perrin, et al., 2008). More specifically, these paradigms circumvent the need for voluntary motor behaviour by relying on neurophysiological indicators of awareness. Therefore, if a patient is able to understand and follow task instructions, by performing the active condition we can assume that he/she retains a certain level of consciousness and volition. In previous active studies using EEG and active protocols, healthy participants and patients were often asked to focus their attention on and count their own name, which was presented auditorily among other names. A larger P3 amplitude for attended own names as compared to unattended names was for example observed in controls as well as in a group of MCS and one LIS patient but not in VS/UWS patients (Schnakers, Perrin, et al., 2008, 2009). This was interpreted as an indicator of voluntary behaviour and, thus, conscious top-down control. This straightforward interpretation of the P3 response has, however, recently been challenged by Silverstein, Snodgrass, Shevrin, and Kushwaha (2015). The authors were able to show that the P3 component can be also elicited by entirely subliminal stimulus presentation and, thus, that specific cognitive processes can occur without consciousness. The interpretation of the presence of a P3 component as an index of conscious processing is, therefore, substantially challenged. In another study, stronger theta event-related synchronization (ERS) as well as alpha event-related desynchronization (ERD) was reported when subjects counted the presentation of the subject's own name (SON) as compared to when participants were merely passively listening to it without a specific instruction (Fellinger et al., 2011). Interestingly, this task-induced (de)synchronization was evident only when the SON was to be counted, but not when participants were asked to count other unfamiliar names (UN). These findings support the notion that, due to its intrinsic emotional content and self-relevance, the SON might be easier to process than other names and may even facilitate the engagement of additional top-down attention (Holeckova, Fischer, Giard, Delpuech, & Morlet, 2006; Höller, Kronbichler, et al., 2011; Mack, Pappas, Silverman, & Gay, 2002; Perrin et al., 2005; Ruby et al., 2013). It has been consistently reported that other emotionally and self-relevant stimuli, such as familiar objects, infant cries or the voice of a family member are strongly processed in a bottom-up manner (Bekinschtein et al., 2004; Di et al., 2007; Jones, Hux, Morton-Anderson, & Knepper, 1994; Laureys, Perrin, & Brédart, 2007; Laureys et al., 2004). Therefore, emotionally relevant information may be easier to process, due to the stronger bottom-up strength, and therefore facilitate the deployment of top-down attention. Emotional stimuli may, thus, be particularly useful in paradigms that use instruction-following manipulations, such as in an active task, in DOC patients (de Jong, Willemsen, & Paans, 1997; Di Stefano, Cortesi, Masotti, Simoncini, & Piperno, 2012; Di et al., 2007; Fellinger et al., 2011; Holeckova et al., 2006; Perrin, Castro, Tillmann, & Luauté, 2015). This adaptation might therefore be crucial in preventing false negative results that is in missing wilful behaviour in non-communicative individuals. This is particularly true as active tasks usually involve a high demand on intact higher cognitive processes such as sustained attention, sensory processing, or remembering the instruction (Kondziella, Friberg, Frokjaer, Fabricius, & Møller, 2015).

The current study adopts a paradigm that has already been validated in healthy controls (del Giudice et al., 2014) and investigates the suitability of such a paradigm for the assessment of individual awareness levels in a first sample of DOC and LIS patients. We adopted the classic own name paradigm including a passive and an active condition (e.g. Schnakers, Perrin, et al., 2008) and additionally varied the familiarity of the voice (i.e. the voice of a familiar person vs. the voice of a stranger) and thus the emotional relevance of the stimuli. The introduction of familiar voices in the active condition, aims at confronting patients with emotionally relevant material, which might capture additional attentional resources, maximize patients' responsiveness and facilitate detection of task relevant stimuli. In the passive condition, participants were presented with their own name as well as other unfamiliar names uttered by both a familiar and a stranger's voice. In the active condition, we only presented UN in order to better differentiate top-down attention (i.e. instruction following and counting) from bottom-up attentional processes, which might be initiated automatically by the presentation of the SON (Perrin, García-Larrea, Mauguière, & Bastuji, 1999; Portas et al., 2000; Wood & Cowan, 1995).

Besides this, we propose that the quantification of EEG responses by means of oscillatory responses (i.e. ERS/ERD) instead of event-related potentials (ERPs) is advantageous. Focusing on oscillatory activity does, contrary to ERPs, account for both induced and time-locked evoked activity and is therefore more sensitive and less prone to temporal dispersion than evoked-potentials (Klimesch, 1999; Mouraux & Iannetti, 2008). Furthermore, it may also circumvent the problem of prevailing delta EEG background activity in DOC patients, which can interfere with ERP detection (Höller, Bergmann, et al., 2011; Kotchoubey et al., 2005; Neumann & Kotchoubey, 2004; Sabri & Campbell, 2002).

Looking at specific frequency bands, is expected to allow us to quantify attentional and memory processes (Klimesch, 1999, 2012; Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998; Petsche, Kaplan, Von Stein, & Filz, 1997) involved in the detection of self-relevant stimuli and instruction following and therefore identify otherwise hidden signs of cognition.

Beyond these considerations, we acknowledge that group analyses in DOC patients are often challenging and little reliable because of the high inter-individual variability of lesion site, extent, brain activity, etc. (Kotchoubey, Lang, Herb, Maurer, & Birbaumer, 2004; Lechinger et al., 2013). In the present paper, we seek to counteract this methodological issue by using a non-parametric single-subject approach.

2. Materials and methods

2.1. Subjects

A total of seven patients participated in the study, four diagnosed with VS/UWS and three with LIS. For each patient, written informed consent was obtained from relatives or legal representatives and the study was approved by the local ethics committee of the Medical University of Graz and Vienna (Austria) and the Cuban Society of Clinical Neurophysiology, Cuba. Formally, DOC patients were diagnosed by two independent raters using the CRS-R (Giacino et al., 2004). Sedative and other centrally acting medication was discontinued and muscle relaxants were reduced to half the active dosage (if any) for the study period. Demographic information, diagnosis and brain damage aetiology is depicted in Table 1. The control sample consisted of 5 males and 9 females (Mean age = 25, 79 ± 8.17). For details on the healthy control sample and their results please also see del Giudice et al. (2014).

2.2. Experimental design and procedure

The objective of this study was to test the applicability of the previously used familiar (voice) SON (fSON) task (del Giudice et al., 2014) in DOC and LIS patients. The SON and five commonly used Austrian names (according to STATISTIK AUSTRIA; http://www.statistik.at/) matched for number of syllables and gender of the participant were presented to each patient. From UN we also excluded names familiar to the patient, i.e. family members or close friends names. The stimulus set was specific for each participant with the mean duration of the stimuli being 791 ms (±121 ms). Stimuli and task instructions were presented via headphones at a sound pressure level of 80 dB. All stimuli were either spoken by a familiar voice (FV; subject's family members or close friends) or unfamiliar voice (UFV; spoken by a text-to-speech algorithm, CereProc®). The task consisted of a passive listening condition and an active counting condition. During the passive condition, patients were asked to just listen to the names presented. In the active condition, they were asked to concentrate and carefully count how many times a specific name was presented (1 target stimulus, 2 non-target stimuli). Instructions were repeated at the beginning of each block (in order to minimize memory demands). In the passive condition, patients were presented with the SON and two different UN, all uttered by a familiar and an unfamiliar voice. The active condition was used to investigate patients' ability to follow instructions; only UN were presented and all were uttered by a familiar voice. The inter stimulus interval [ISI] was set to 2000 ms and Presentation® software (Version 0.71; Presentation Software, Neurobehavioral Systems Inc., California) was used for stimulus presentation and synchronization. Each condition consisted of three blocks, with each block including 13 random presentations of each name. For additional details about block duration and study design please refer to del Giudice et al. (2014). Prior to each block, patients were – if necessary – briefly stimulated in order to ensure a sufficient arousal level. All blocks were performed during times when patients had their eyes open to make sure they were awake.

2.3. Data acquisition

The EEG was recorded at bedside using 32 Ag/AgCl electrodes with BrainAmp EEG amplifier (BrainProducts® GmbH, Gilching, Germany) and Brain Vision Recorder (Brain Products®) in Austria and with MEDICID 05 system (Neuronic SA, Havana, Cuba) in Cuba. The EEG sampling rate was set to 500 Hz and impendences were kept below 5 kΩ. The setup consisted of 26 scalp, four electrooculogram (EOG) (two vertical and two horizontal) and two electromyogram (EMG) electrodes. Scalp positions were FP1, FP2, F3, Fz, F4, FC3, FC4, C5, C3, Cz, C4, C6, CP3, CP4, P3, Pz, P4, PO7 and PO8 placed according to the international 10–20 system. FCz served as active reference, and electrodes for later re-referencing were placed on left and right mastoids. During the recording the patients' upper body was brought to an up-right position.

Table 1
Demographic data of patients. CRS-R: Coma Recovery Scale - Revised; LIS: Locked-in syndrome; VS/UWS: Vegetative State/Unresponsive Wakefulness Syndrome or Chronic Vegetative State/Unresponsive Wakefulness Syndrome VS/UWS; HM*: In this patient CRS-R assessment was performed after EEG testing. In GCS, the asterisk for the 2nd assessment denotes the mean of the total score on three different days; Patient CF was reported with a history of chronic polysubstance dependence according to DSM - IV TR classification (Association, 2000). CPR: Cardiopulmonary resuscitation.

Patient ID	Age	Gender	Time since injury	Clinical diagnosis	CRS-R scores								Aetiology
					Audio 1st ass.	Visual 1st ass.	Motor 1st ass.	Oromotor 1st ass.	Communication 1st ass.	Arousal 1st ass.	Total 1st ass.	Total 2nd ass.	
ITM	21	F	1 year	LIS	4	5	3	0	2	3	17	17	Hemangioblastoma tumor, surgical treatment brain steam
HM*	65	M	8 months	LIS	2	3	2	1	1	2	11	11	Basilaris thrombosis/Pons infarct
RCT	46	M	7 month	LIS	4	5	3	2	2	3	19	19	Stroke of the brainstem
GCS	53	M	5 years	VS/UWS	1	1	2	1	0	2	7	5*	Cardiac arrest anesthetic accident
CF	30	M	5 years	VS/UWS	1	0	1	0	0	2	4	4	Cerebral hypoxia after tracheostomy
JS	65	F	4 months	VS/UWS	1	0	1	2	0	2	6	4	CPR after cardiac arrest Global cerebral Ischemia
PRG	24	F	16 month	VS/UWS	1	0	2	1	0	2	6	6	Traumatic brain injury

2.4. Data analyses

In a first step, we re-referenced data to average mastoids and bandpass filtered between 0.5 and 40 Hz. Ocular correction was conducted using the regression-based approach from Gratton, Coles, and Donchin (1983) implemented in BrainVision Analyzer 2.0 (Brain Products, Gilching, Germany).

Afterwards, data were visually checked for residual artefacts and only artefact-free trials were included in further analyses. Data were then segmented into epochs ranging from −1200 to +1800 ms relative to stimulus onset. EEG segments for each condition of interest were then exported and analysed using own-built Matlab routines (MathWorks, Natick, MA) and the EEGLAB toolbox (Delorme & Makeig, 2004).

To characterize oscillatory activity correlated with the presentation of different auditory stimuli we used the event-related spectral perturbation (ERSP) method as implemented in EEGLAB (Delorme & Makeig, 2004) which is comparable with the classical ERS/ERD method (Pfurtscheller & Aranibar, 1977). Note that in the following, positive values reflect an increase in oscillatory activity from before to after stimulus onset, whereas negative values reflect a decrease. Event-related changes in spectral EEG power from before to after stimulus appearance were calculated for frequencies ranging from 1 to 30 Hz. ERSP computation was performed using a two-cycle Morlet wavelets with an increasing factor of 0.8. As a reference period, the time period between −700 to and 200 ms before stimulus onset was chosen. Baseline correction was computed using the subtraction method by Hu, Xiao, Zhang, Mouraux, and Iannetti (2014); this subtraction approach is unbiased and allows minimizing the dominance of low frequency EEG power.

We focused on theta (4–7 Hz) and alpha (8–12 Hz) frequency bands as in our previous study on healthy controls (del Giudice et al., 2014). In the present study including patients with various brain pathologies only alpha effects varied systematically with the task manipulation. For this reason we focus on the statistical analysis of alpha frequencies only.

Frequency spectra for active and passive conditions in the task are illustrated in Supplementary Fig. 1. EEG frequency spectra are often slowed in DOC patients and typically lack a clear alpha peak. For frequency plots analyses all artefacts free EEG periods during the experimental conditions (active and passive) were divided into 2 s epochs and fast Fourier transformed.

2.5. Statistical analyses

Statistical analyses were performed using the Matlab Statistics toolbox and EEGLAB's statistics toolkit. Grand averages for each subject were used to compute statistical analyses of our hypotheses in healthy controls while, importantly, a single-trial approach was adopted for patients. Non-parametric permutation (with 2000 permutations) tests were used in order to identify regions that showed significant differences in ERSP between the different stimulation conditions: ACTIVE, PASSIVE NAME and PASSIVE VOICE.

The permutation test has several advantages over parametric statistical tests (Maris & Oostenveld, 2007; Nichols & Holmes, 2002), which is that it controls for multiple comparisons since all the time frequencies elements are permuted in parallel and makes minimal prior assumptions. Thus, the non-parametric permutation test thus can be applied even in situations where the assumptions of parametric approaches are not met (or cannot be verified) and is considered a powerful approach for analysis of single-subject data.

Statistical analyses were performed with the maximum available number of artefact-free trials for each condition and for each subject (passive condition: 18–38 trials, active condition: 27–39 trials).

3. Results

3.1. Alpha response in the passive listening condition

3.1.1. Previous results in controls (group level)

In the following paragraph we will briefly summarize significant results from healthy controls already published in del Giudice et al. (2014). Alpha band results for the passive condition are reported for the group mean. Individual subjects' result can be found in the supplementary material of del Giudice et al. (2014).

Analyses revealed significant differences between FV and UV over P4 ($t(13) = -2.16$, $p < 0.05$) Cz ($t(13) = -2.16$, $p < 0.05$) and between SON and UN over P4 electrodes ($t(13) = -2.10$, $p < 0.05$) indicating stronger alpha desynchronization after the presentation of self-relevant stimuli over the right hemisphere (cf. Fig. 1).

3.1.2. Single patient analyses

3.1.2.1. ITM: a 21 year old female with Locked-in Syndrome since 1 year. Analyses revealed significant differences between FV and UV over electrodes F3 ($t(37) = -2.59$, $p < 0.05$) and C5 ($t(37) = -2.17$, $p < 0.05$) indicating higher alpha desynchronization after the presentation of FV over the left frontal area. No significant differences were evident for the factor NAME (cf. Fig. 1). For interaction effects please see Suppl. Fig. 2.

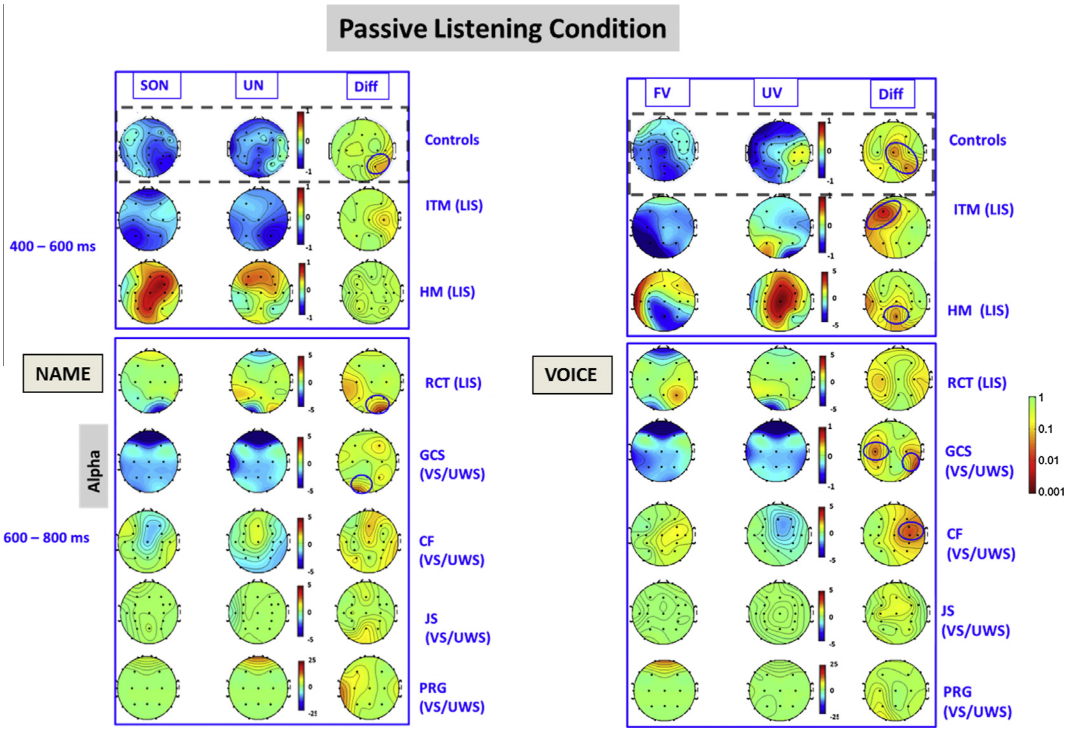

Fig. 1. Topographic distribution of EEG alpha responses in the passive condition. Passive NAME contrast (SON vs. UN) and passive VOICE contrast (FV vs. UV) as well as the (color-coded) statistical difference between the two conditions. Please note that we plot the strongest observed effects in alpha, which are between 400 and 600 ms for two LIS patients (ITM and HM) and delayed (600 and 800 ms) for the other VS/UWS as well as one LIS patient. All time windows always refer to time after stimulus onset. Cold colors (blue) indicate desynchronization with respect to the baseline (−700 to −200 ms) and circles mark statistically significant differences between the conditions. In addition we depicted alpha event-related spectral perturbation (ERSP) in healthy controls for comparison of what to expect for the utilized fSON task. Abbreviations: subject's own name [SON]; unfamiliar name [UN], Familiar voice [FV]; unfamiliar voice [UFV]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.1.2.2. HM: A 65 year old man with Locked-in Syndrome since 6 months. Results revealed significant differences between FV and UV over electrode Pz ($t(24) = -2.08$, $p < 0.05$) indicating that the FV is enhancing higher alpha desynchronization as compared to the unfamiliar voice. No significant differences were evident for the factor NAME (cf. Fig. 1).

3.1.2.3. RCT: a 46 year old man with Locked-in Syndrome since 7 months. No significant differences were evident for the factor VOICE. Analysis revealed a statistically significant difference for the factor NAME indicating stronger alpha desynchronization over PO8 after the presentation of the SON relative to the UN ($t(37) = 2.22$, $p < 0.05$) (cf. Fig. 1).

3.1.2.4. GCS: a 53 year old man being in VS/UWS since 5 years. Statistical analyses revealed in the VOICE condition a significant difference on C3 ($t(37) = -2.25$, $p < 0.05$) for the factor VOICE indicating that the FV enhances higher alpha desynchronization compared to the unfamiliar one. At CP6, the UV triggered higher alpha desynchronization ($t(37) = 2.59$, $p < 0.05$). For the factor NAME higher alpha desynchronization was evident for the SON as compared to the UN at PO7 ($t(37) = 3.52$, $p < 0.05$) (cf. Fig. 1).

3.1.2.5. CF: A 30 year old male being in VS/UWS since 5 years. In the passive condition, significant differences were observed over the right side of the scalp (FC4 ($t(37) = 2.18$, $p < 0.05$)), C4 ($t(37) = 2.43$, $p < 0.05$) and C6 ($t(37) = 2.11$, $p < 0.05$) for the factor VOICE. Specifically, UV triggered higher alpha desynchronization as compared to the FV (see Fig. 1 for scalp distribution). No significant differences were evident for the factor NAME.

3.2. Alpha response in the active counting condition

3.2.1. Previous results in controls (group level)

Results in the active condition indicated significant differences between target and non-target over electrodes CPz ($t(13) = -4.00$, $p < 0.05$) P3 ($t(13) = -4.48$, $p < 0.05$) Pz ($t(13) = -5.03$, $p < 0.05$) and POz ($t(13) = -5.17$, $p < 0.05$) (cf. Fig. 2).

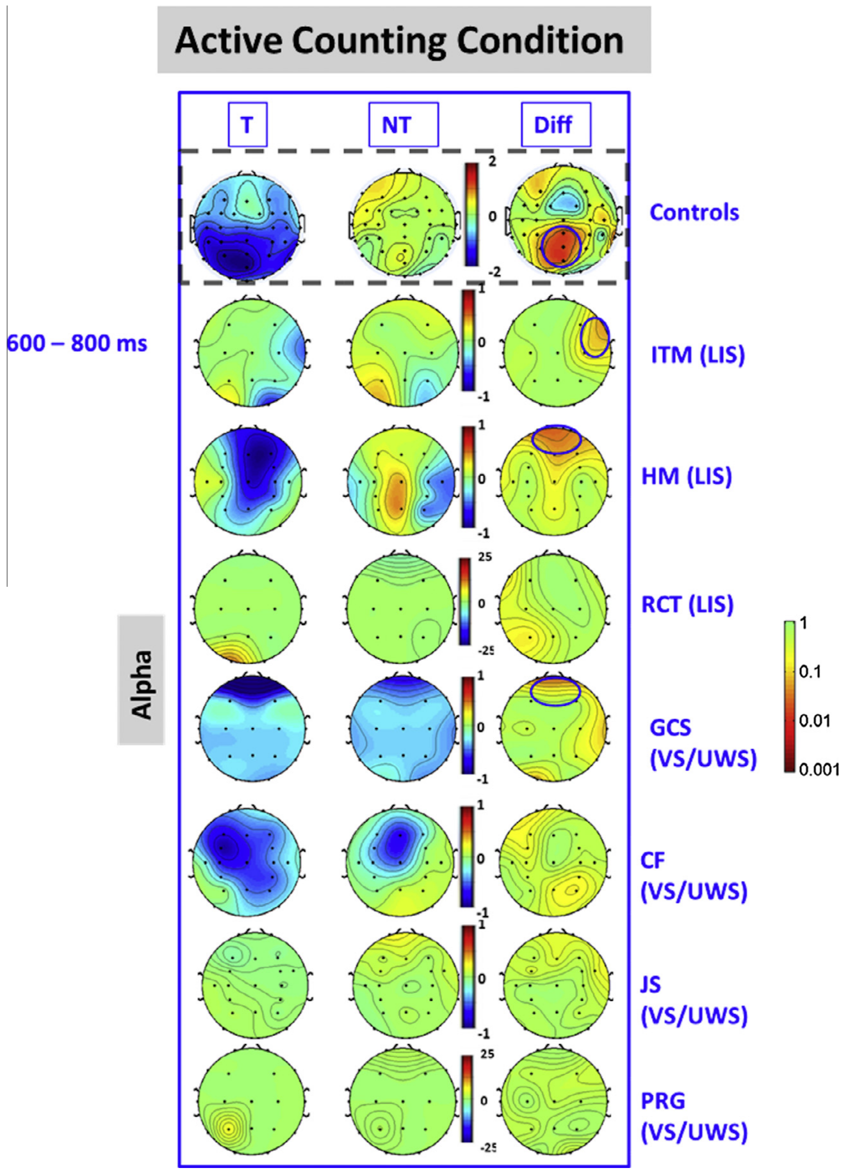

Fig. 2. Topographic distribution of the alpha response with respect to target processing. Note that 2 out of 3 LIS patients (66%) and 1 out of 4 UWS patients (25%) exhibit significant effects in the alpha range. Target names (left) non-target (right) as well as the (color-coded) statistical difference between the two conditions are reported in the figure. For illustrative purpose the strongest observed effects in alpha, which are between 400 and 600 ms for two LIS patients (ITM and HM) and delayed in time (600 and 800 ms) for the other VS/UWS as well as one LIS patient are plotted. All time windows always refer to time after stimulus onset. Cold colors (blue) indicate desynchronization with respect to the baseline (−700 to −200 ms) and circles mark statistically significant differences between the conditions. For comparison the scalp distribution for controls in the active condition is shown at top. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2.2. Single patient analyses

3.2.2.1. ITM. The difference between target and non-target was significant at FC4 ($t(37) = 2.05$, $p < 0.05$) indicating more pronounced alpha desynchronization for target stimuli (cf. Fig. 2).

3.2.2.2. HM. The comparison between target and non-target yielded significant differences over the frontal areas (FP1 ($t(29) = -2.38$, $p < 0.05$) and FP2 ($t(29) = -2.31$, $p < 0.05$)) with higher alpha desynchronization for target stimuli (cf. Fig. 2).

3.2.2.3. GCS. In the active condition, we observed statistically significant differences over the frontal area (FP1 ($t(38) = -2.35$, $p < 0.05$) and FP2 ($t(38) = -2.35$, $p < 0.05$)) suggesting that for this patient the presentation of the target increased alpha power desynchronization (cf. Fig. 2).

4. Discussion

The present study aimed at testing and validating previous findings from healthy controls, with regard to information processing benefits associated with salient stimuli, in a first sample of patients. Specifically, we tested the power of a familiar stimulus such as the mother's voice on the processing of first names.

Interestingly, it is revealed that the familiar voice seems to be more salient than the subject's own name itself, with two LIS and two VS/UWS patients showing stronger alpha responses to the relative's voice. Furthermore, in the more demanding "active condition" only two LIS and one VS/UWS patient could consistently attend to the target name.

More specifically, the passive condition focused on two contrasts, namely own name vs. other name and familiar vs. unfamiliar voice processing. When looking at the differences between own and other names, most of the patients did not show any systematic change in the amount of alpha desynchronization (cf. Fig. 1, left column). Especially the non-significant response of the two LIS patients (ITM and HM) are surprising. While patient ITM shows systematic alpha desynchronization to both names, patient HM shows an unexpected alpha synchronization to the subject own name. Latter might be related to a lack of sensitivity of the task as the chosen own name might not have been salient to the patient (e.g. not the habitual nickname used in the clinic), or the exact underlying brain pathology which would resemble the paradoxical alpha synchronization observed earlier for MCS patients (Schabus et al., 2011). The other surprising finding is the VS/UWS patient (GCS) who shows a statistical difference in alpha in reaction to the processing of own vs. other names. Interestingly this is also the only VS/UWS patient which is showing a response in the active condition when asked to count a specific target name and might therefore be a misdiagnosed MCS patient. Stronger alpha desynchronization in response to the own name, this has been previously associate, where we previously were able to show that higher occipital alpha desynchronization was associated to the activation of long-term autobiographical memory traces (del Giudice et al., 2014; Fellinger et al., 2011; Klimesch, 1996; Klimesch, Sauseng, & Hanslmayr, 2007; Tamura, Karube, Mizuba, & Iramina, 2012). Therefore, we can speculate that this may have been the case also for patients.

The own name paradigm can be considered as part of the more general domain of "self" processing and especially self-awareness. For example, the own face has been shown to be likewise processed preferentially with even MCS patients responding stronger to their own face as compared to other faces (Bagnato, Boccagni, Prestandrea, & Galardi, 2015; Laureys et al., 2007). Yet, in the present study it appears that the own name was not very efficient in evoking a stronger processing as observed earlier in healthy individuals. Besides the own name also the voice of a familiar person is carrying specific relevance in the social context and is therefore preferentially processed.

Focusing on the difference between familiar and unfamiliar voices (cf. Fig. 1, right) it becomes evident that the perceived relevance or inherent processing of these familiar voice stimuli is stronger than for the own name. Specifically, two out of the three LIS patients (ITM and HM), as well as two of the four VS/UWS patients (GCS and CF) responded with a differential alpha response. All but patient CF showed stronger alpha desynchronization after the familiar voice presentation, as would be expected for a stronger processed stimulus which is released from inhibition once identified as relevant. Indeed we are lacking a conclusive explanation why patients like CF in the voice condition or ITM and HM in the name condition are showing these unusual brain patterns. We believe that this might be related to the arousal fluctuations well known for these patients or inconsistent EEG patterns given the limited signal to noise ratio in many of these recordings. Furthermore, the LIS patient (RCT) did not show any systematic change in response to the familiar voice or the presentation of the target name. This patient also had limited emotional control due to persistent pain on the day of recording (with repeated periods of crying), which might have reduced his overall compliance with task instructions. To overcome this limitation, we suggest that future protocols should consider to repeatedly assess the same patients with an identical EEG protocol and to consider the time of day when the patients might be well-rested and more likely responsive. This also applies to the bedside diagnosis which is known to fluctuate over the day (Cortese et al., 2015).

In the active condition, where patients were listening to only unfamiliar names but spoken by a familiar voice, we observed that the same three patients previously showing stronger alpha desynchronization to the more salient relative's voice stimulus were able to follow instructions and focus attention on the target name. Specifically, LIS patients ITM and HM again show stronger alpha desynchronization to the target, as well as VS/UWS patient GCS. In line with this is the established finding of alpha desynchronizes in conditions requiring attentional processing (Klimesch, 2012; Klimesch et al., 1998; Petsche et al., 1997; Sauseng et al., 2005).

We also would like to shortly comment on the absent theta findings in the present study which might seem contradictory to earlier published results (del Giudice et al., 2014; Fellinger et al., 2011). The absence of theta differences between target and non-targets might be related to two facts. In our earlier studies in patients (Fellinger et al., 2011) theta synchronization was only evident when patients were focusing on the own name in the active condition, whereas comparable to our results, there was no such difference for unfamiliar stimuli (cf. Fellinger et al., 2011, Fig. 2b). In our later study using healthy controls (del Giudice et al., 2014) we only could reveal such a theta effect when focusing on hemispheric asymmetries which we did not do in the present study.

Open questions to be addressed in future studies include (i) the further exploration and verification of the unexpected EEG effects in some of the DOC patients (e.g., by repeating the same paradigm in patients and potentially across different times of day) (ii) and a considerable extension of the clinical sample presented here and including MCS patients. The utilization of computer generated non-human spoken stimuli (as used here) could be discussed as a further issue, yet given the quality of this sophisticated material we do not considers this as a matter of concern.

5. Conclusions

Assessing residual cognitive abilities and awareness in patients who are not able to express themselves (verbally or behaviourally) is inherently difficult. Salient stimuli, such as the familiar voice of a relative, may boost information processing and increase the likelihood of observing meaningful behaviour in such patients. EEG and especially oscillatory brain activity would be a cheap and ambulatory alternative for identifying such behaviour in clinics and rehabilitation centres worldwide. In the current study the ability of one of our VS/UWS patients to follow instructions highlight the importance to not rely solely on behavioural sign of consciousness at bedside but to complement this diagnosis with neuroscientific evidence whenever possible.

Conflict of interest

The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.concog.2016.06.013.

References

Andrews, K., Murphy, L., Munday, R., & Littlewood, C. (1996). Misdiagnosis of the vegetative state: Retrospective study in a rehabilitation unit. *BMJ: British Medical Journal, 313*(7048), 13.
American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders DSM-IV-TR* (4th ed. (Text Revision)). American Psychiatr.
Bagnato, S., Boccagni, C., Prestandrea, C., & Galardi, G. (2015). Autonomic correlates of seeing one's own face in patients with disorders of consciousness. *Neuroscience of Consciousness, 2015*(1), niv005.
Bekinschtein, T., Niklison, J., Sigman, L., Manes, F., Leiguarda, R., Armony, J., ... Olmos, L. (2004). Emotion processing in the minimally conscious state. *Journal of Neurology, Neurosurgery & Psychiatry, 75*(5), 788.
Bruno, M.-A., Gosseries, O., Ledoux, D., Hustinx, R., & Laureys, S. (2011). Assessment of consciousness with electrophysiological and neurological imaging techniques. *Current Opinion in Critical Care, 17*(2), 146–151.
Cortese, M., Riganello, F., Arcuri, F., Pugliese, M., Lucca, L., Dolce, G., & Sannita, W. (2015). Coma recovery scale-r: Variability in the disorder of consciousness. *BMC Neurology, 15*(1), 1.
Cruse, D., Chennu, S., Chatelle, C., Bekinschtein, T. A., Fernández-Espejo, D., Pickard, J. D., ... Owen, A. M. (2012). Bedside detection of awareness in the vegetative state: A cohort study. *The Lancet, 378*(9809), 2088–2094.
Cruse, D., Monti, M. M., & Owen, A. M. (2011). Neuroimaging in disorders of consciousness: Contributions to diagnosis and prognosis. *Future Neurology, 6*(2), 291–299.
de Jong, B. M., Willemsen, A., & Paans, A. (1997). Regional cerebral blood flow changes related to affective speech presentation in persistent vegetative state. *Clinical Neurology and Neurosurgery, 99*(3), 213–216.
del Giudice, R., Lechinger, J., Wislowska, M., Heib, D. P., Hoedlmoser, K., & Schabus, M. (2014). Oscillatory brain responses to own names uttered by unfamiliar and familiar voices. *Brain Research, 1591*, 63–73.
Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*(1), 9–21.
Di Stefano, C., Cortesi, A., Masotti, S., Simoncini, L., & Piperno, R. (2012). Increased behavioural responsiveness with complex stimulation in VS and MCS: Preliminary results. *Brain Injury, 26*(10), 1250–1256.
Di, H., Yu, S., Weng, X., Laureys, S., Yu, D., Li, J., ... Chen, Y. (2007). Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology, 68*(12), 895–899.
Fellinger, R., Klimesch, W., Schnakers, C., Perrin, F., Freunberger, R., Gruber, W., ... Schabus, M. (2011). Cognitive processes in disorders of consciousness as revealed by EEG time–frequency analyses. *Clinical Neurophysiology, 122*(11), 2177–2184.
Giacino, J. T., Kalmar, K., & Whyte, J. (2004). The JFK Coma Recovery Scale-Revised: Measurement characteristics and diagnostic utility. *Archives of Physical Medicine and Rehabilitation, 85*(12), 2020–2029.
Giacino, J., Zasler, N., Whyte, J., Katz, D., Glen, M., & Andary, M. (1995). Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness. *Archives of Physical Medicine and Rehabilitation, 76*(2), 205–209.
Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology, 55*(4), 468–484.
Holeckova, I., Fischer, C., Giard, M.-H., Delpuech, C., & Morlet, D. (2006). Brain responses to a subject's own name uttered by a familiar voice. *Brain Research, 1082*(1), 142–152.
Höller, Y., Bergmann, J., Kronbichler, M., Crone, J. S., Schmid, E. V., Golaszewski, S., & Ladurner, G. (2011). Preserved oscillatory response but lack of mismatch negativity in patients with disorders of consciousness. *Clinical Neurophysiology, 122*(9), 1744–1754.

Höller, Y., Kronbichler, M., Bergmann, J., Crone, J. S., Ladurner, G., & Golaszewski, S. (2011). EEG frequency analysis of responses to the own-name stimulus. *Clinical Neurophysiology, 122*(1), 99–106.
Hu, L., Xiao, P., Zhang, Z., Mouraux, A., & Iannetti, G. D. (2014). Single-trial time–frequency analysis of electrocortical signals: Baseline correction and beyond. *NeuroImage, 84*, 876–887.
Jones, R., Hux, K., Morton-Anderson, K. A., & Knepper, L. (1994). Auditory stimulation effect on a comatose survivor of traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 75*(2), 164.
Klimesch, W. (1996). Memory processes, brain oscillations and EEG synchronization. *International Journal of Psychophysiology, 24*(1), 61–100.
Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews, 29*(2), 169–195.
Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences, 16*(12), 606–617.
Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., & Schwaiger, J. (1998). Induced alpha band power changes in the human EEG and attention. *Neuroscience Letters, 244*(2), 73–76.
Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition–timing hypothesis. *Brain Research Reviews, 53*(1), 63–88.
Kondziella, D., Friberg, C. K., Frokjaer, V. G., Fabricius, M., & Møller, K. (2015). Preserved consciousness in vegetative and minimal conscious states: Systematic review and meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*. http://dx.doi.org/10.1136/jnnp-2015-310958.
Kotchoubey, B., Lang, S., Herb, E., Maurer, P., & Birbaumer, N. (2004). Reliability of brain responses to a person's own name in healthy subjects and patients with brain damage. In *Brainwaves and mind: Recent advances* (pp. 75–80). New York: Kiellberg.
Kotchoubey, B., Lang, S., Mezger, G., Schmalohr, D., Schneck, M., Semmler, A., ... Birbaumer, N. (2005). Information processing in severe disorders of consciousness: Vegetative state and minimally conscious state. *Clinical Neurophysiology, 116*(10), 2441–2453.
Laureys, S., Celesia, G., Cohadon, F., Lavrijsen, J., León-Carrión, J., Sannita, W., ... Zeman, A. (2010). Unresponsive wakefulness syndrome: A new name for the vegetative state or apallic syndrome. *BMC Medicine, 8*(1), 68.
Laureys, S., Gosseries, O., & Tononi, G. (2015). *The neurology of consciousness: Cognitive neuroscience and neuropathology*. Academic Press.
Laureys, S., Owen, A. M., & Schiff, N. D. (2004). Brain function in coma, vegetative state, and related disorders. *Lancet Neurology, 3*(9), 537–546. Retrieved from<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15324722>.
Laureys, S., Perrin, F., & Brédart, S. (2007). Self-consciousness in non-communicative patients. *Consciousness and Cognition, 16*(3), 722–741.
Lechinger, J., Chwala-Schlegel, N., Fellinger, R., Donis, J., Michitsch, G., Pichler, G., & Schabus, M. (2013). Mirroring of a simple motor behavior in Disorders of Consciousness. *Clinical Neurophysiology, 124*(1), 27–34.
Mack, A., Pappas, Z., Silverman, M., & Gay, R. (2002). What we see: Inattention and the capture of attention by meaning. *Consciousness and Cognition, 11*(4), 488–506.
Maris, E., & Oostenveld, R. (2007). Nonparametric statistical testing of EEG-and MEG-data. *Journal of Neuroscience Methods, 164*(1), 177–190.
Monti, M. M., Vanhaudenhuyse, A., Coleman, M. R., Boly, M., Pickard, J. D., Tshibanda, L., ... Laureys, S. (2010). Willful modulation of brain activity in disorders of consciousness. *New England Journal of Medicine, 362*(7), 579–589.
Mouraux, A., & Iannetti, G. D. (2008). Across-trial averaging of event-related EEG responses and beyond. *Magnetic Resonance Imaging, 26*(7), 1041–1054.
Neumann, N., & Kotchoubey, B. (2004). Assessment of cognitive functions in severely paralysed and severely brain-damaged patients: Neuropsychological and electrophysiological methods. *Brain Research Protocols, 14*(1), 25–36.
Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping, 15*(1), 1–25.
Owen, A. M., Coleman, M. R., Boly, M., Davis, M. H., Laureys, S., & Pickard, J. D. (2006). Detecting awareness in the vegetative state. *Science, 313*(5792), 1402.
Owen, A. M., Schiff, N. D., & Laureys, S. (2009). A new era of coma and consciousness science. *Progress in Brain Research, 177*, 399–411.
Perrin, F., Castro, M., Tillmann, B., & Luauté, J. (2015). Promoting the use of personally relevant stimuli for investigating patients with disorders of consciousness. *Frontiers in Psychology, 6*.
Perrin, F., García-Larrea, L., Mauguière, F., & Bastuji, H. (1999). A differential brain response to the subject's own name persists during sleep. *Clinical Neurophysiology, 110*(12), 2153–2164.
Perrin, F., Maquet, P., Peigneux, P., Ruby, P., Degueldre, C., Balteau, E., ... Laureys, S. (2005). Neural mechanisms involved in the detection of our first name: A combined ERPs and PET study. *Neuropsychologia, 43*(1), 12–19.
Petsche, H., Kaplan, S., Von Stein, A., & Filz, O. (1997). The possible meaning of the upper and lower alpha frequency ranges for cognitive and creative tasks. *International Journal of Psychophysiology, 26*(1–3), 77–97.
Pfurtscheller, G., & Aranibar, A. (1977). Event-related cortical desynchronization detected by power measurements of scalp EEG. *Electroencephalography and Clinical Neurophysiology, 42*(6), 817–826.
Portas, C. M., Krakow, K., Allen, P., Josephs, O., Armony, J. L., & Frith, C. D. (2000). Auditory processing across the sleep-wake cycle: Simultaneous EEG and fMRI monitoring in humans. *Neuron, 28*(3), 991–999.
Ruby, P., Blochet, C., Eichenlaub, J.-B., Bertrand, O., Morlet, D., & Bidet-Caulet, A. (2013). Alpha reactivity to complex sounds differs during REM sleep and wakefulness. *PLoS One, 8*(11), e79989.
Sabri, M., & Campbell, K. B. (2002). The effects of digital filtering on mismatch negativity in wakefulness and slow-wave sleep. *Journal of Sleep Research, 11*(2), 123–127.
Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., ... Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience, 22*(11), 2917–2926.
Schabus, M., Pelikan, C., Chwala-Schlegel, N., Weilhart, K., Roehm, D., Donis, J., ... Klimesch, W. (2011). Oscillatory brain activity in vegetative and minimally conscious state during a sentence comprehension task. *Functional Neurology, 26*(1), 31.
Schnakers, C., Majerus, S., Goldman, S., Boly, M., Van Eeckhout, P., Gay, S., ... Moonen, G. (2008). Cognitive function in the locked-in syndrome. *Journal of Neurology, 255*(3), 323–330.
Schnakers, C., Perrin, F., Schabus, M., Hustinx, R., Majerus, S., Moonen, G., ... Laureys, S. (2009). Detecting consciousness in a total locked-in syndrome: An active event-related paradigm. *Neurocase, 15*(4), 271–277.
Schnakers, C., Perrin, F., Schabus, M., Majerus, S., Ledoux, D., Damas, P., ... Moonen, G. (2008). Voluntary brain processing in disorders of consciousness. *Neurology, 71*(20), 1614–1620.
Schnakers, C., Vanhaudenhuyse, A., Giacino, J., Ventura, M., Boly, M., Majerus, S., ... Laureys, S. (2009). Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology, 9*(1), 35.
Silverstein, B. H., Snodgrass, M., Shevrin, H., & Kushwaha, R. (2015). P3b, consciousness, and complex unconscious processing. *Cortex, 73*, 216–227.
Tamura, K., Karube, C., Mizuba, T., & Iramina, K. (2012). ERP and time frequency analysis of response to subject's own name. In *Paper presented at the biomedical engineering international conference (BMEiCON), 2012*. .
Wood, N., & Cowan, N. (1995). The cocktail party phenomenon revisited: How frequent are attention shifts to one's name in an irrelevant auditory channel? *Journal of Experimental Psychology: Learning, Memory, and Cognition, 21*(1), 255.